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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,343	03/05/2007	Yasuharu Nishimura	P29875	4864
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EXAMINER				
BRISTOL, LYNN ANNE				
ART UNIT		PAPER NUMBER		
1643				
NOTIFICATION DATE		DELIVERY MODE		
08/25/2009		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/577,343

Applicant(s)

NISHIMURA ET AL.

Examiner

LYNN BRISTOL

Art Unit

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 7 and 8 is/are pending in the application.
- 4a) Of the above claim(s) 1 and 2 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3-5, 7 and 8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 1-5, 7 and 8 are all the pending claims in this application.
2. Claim 3 was amended in the Response of 8/4/09.
3. Claims 1 and 2 are withdrawn.
4. Claims 3-5, 7 and 8 are all the pending claims under examination.
5. This Office Action contains new grounds for rejection. This finality of this Office Action is withdrawn.

Election/Restriction

6. The examiner has re-reviewed the prosecution history and noted that Applicants response to the Restriction Requirement of 6/17/08 was incomplete. In their Reply, they failed to elect the diagnostic agent species much less traverse the speciation for the diagnostic agent set forth on p. 5 of the Office Action of 6/17/08.
7. To advance prosecution on the merits and for purposes of record, the examiner has withdrawn the election of species requirement.

Withdrawal of Rejections

Claim Rejections - 35 USC § 103

8. The rejection of Claims 3-5, 7 and (new Claim 8) under 35 U.S.C. 103(a) as being unpatentable over Katagiri et al. (20030165954; published 9/4/03; filed January 9, 2003) in view of Desai et al. (J. Med. Genet. 35:476-481 (1998)) as evidenced by

Nakatsura et al. (Clin. Can. Res. 10:6612-6621 (10/1/2004); cited in the PTO 892 form of PTO 892 form of 6/17/08) is withdrawn.

Applicants' allegations on pp. 4-9 of the Response of 8/4/09 have been considered and are considered persuasive. Applicants allege "neither Katagiri et al. nor Desai et al. teach any correlation between melanoma and GPC3, there cannot be any possible expectation of success in the present method base on those teachings. That is, a person skilled in the art could not possibly read Katagiri et al. and Desai et al. and conclude that there could be any success whatsoever in a diagnostic test for melanoma comprising detecting or measuring GPC3 in a sample from a subject believed to be at risk of malignant melanoma"; Nakatsura et al. is not prior art and the Office is not entitled to rely on it to establish motivation or expectation of success."

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3-5, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps for measuring GPC3

either intracellular (also genomic DNA), extracellular or secreted and the means for measuring the GPC3.

b) Claims 3-5, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps(s) comprising the control sample or GPC3 standard (e.g., protein, nucleic acid) against which any amount of GPC3 in the form of protein or nucleic acid is detected, measured and/or quantitated from a subject sample in order to assess whether the amount is indicative or predictive that the subject is at risk of malignant melanoma. For example, the specification teaches that GPC3 protein is highly expressed in 17/21 melanoma cases and 10/11 pigmented nevus cases (p. 16, Example 4), and therefore, a control cell/standard would seemingly be required to distinguish a melanoma from a pigmented nevus.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

10. Claims 3-5, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting soluble or membrane associated GPC3 protein using an antibody recognizing an extracellular domain of the protein (e.g., 303-464) in a method for diagnosing (or at risk of having) malignant melanoma along

with other clinically relevant melanoma tumor markers (e.g., 5-S-CD and MIA), does not reasonably provide enablement for practicing a diagnostic method using any anti-GPC3 antibody directed to any epitope on the protein and in the absence additional art-recognized melanoma biomarkers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to a method for diagnosing a malignant melanoma comprising detecting or measuring GPC3 in a sample from a subject at risk of having the cancer (Claim 3), where the sample of Claim 3 is contacted with an anti-GPC3 antibody (Claim 4), or where the method of Claim 3 comprises quantifying GPC3 in a sample (Claim 5), or where the antibody of Claim 4 comprises quantifying GPC3 in a sample (Claim 7). Claim 8 is interpreted as being drawn to a method for diagnosing a malignant melanoma comprising a kit comprising an anti-GPC3 antibody.

The relative skill required to practice the invention is a clinical diagnostician performing clinical histological diagnostic assays.

Disclosure in the Specification

The specification teaches and demonstrates detecting and quantifying GPC3 protein in histological sections from melanoma subjects (Example 4) and serum samples from malignant melanoma subjects (Example 5) using the commercially available antibody, 303-464.

For example, for histology, samples from melanoma, pigmented nevus and normal skin regions were compared using the immunohistology technique described in Nakatsura et al. (Biochem. Biophys. Res. Commun. 281, 936-944 (2001); cited in the IDS of 11/13/07). Figure 2 shows that GPC3 protein is highly expressed in 17/21 melanoma cases and 10/11 pigmented nevus cases (p. 16, Example 4), but the specification does not describe a positive/negative control marker and therefore, a control/standard would seemingly be required to distinguish a melanoma from a pigmented nevus.

For ELISA detection of GPC3 protein in sera from melanoma patients (Example 5; Figure 4), the 303-464 was used to coat plates and another commercial biotinylated rabbit polyclonal anti-GPC3 antibody was used to detect the protein in sera. For these studies, samples were obtained from patients' whose profiles were collected from medical records and then clinical stages were determined based on the TNM classification. The amounts of the GPC3 protein in sera was compared with the

melanoma biomarkers, 5-S-CD and MIA, and correlated with melanoma staging from Stage 0-IV.

The ordinary artisan could not practice the method to reliably, reproducibly and predictably diagnose a subject suspected of being at risk for malignant melanoma absent the use of specific control reagents and control samples. The ordinary artisan would not have been enabled to practice the instant method at the time of the invention because the scope of the claims excludes several steps and reagents required to make a clinical immunoassay/histological diagnosis for melanoma. Claim 3 embraces measurement of GPC3 protein by any method, either intracellular, extracellular or secreted and the means to measure GPC3 is not even defined. The claimed antibodies against GPC3 are not clearly defined. It is clear from the specification that an antibody used in the working methods recognizes soluble parts/fragments of GPC3. Glypican 3 is however a membrane bound protein. Thus, only antibodies against secreted/soluble GPC3 can be used in the claimed method. The antibodies against GPC3 should be specified and they are not. The specification teaches that the detection of soluble forms of human GPC3 in serum samples of patients pre-diagnosed with melanoma is important for the present diagnostic method, i.e. to diagnose malignant melanoma in an early state compared to prior art diagnostic methods. However, the only biomarker considered in the entire diagnostic method is GPC3 and the ordinary artisan cannot even practice the instant claimed method without discriminating a melanoma from a heavily pigmented nevus. Thus the claims do not meet the how-to-practice requirement under the enablement analysis.

Prior Art Status: Immunohistology detection of melanoma requires
standardization

Smith et al. (Vet. Pathol. 39:651-678 (2002)) teach prior to the invention filing date the immunohistology is a critical "ancillary diagnostic method" for differentiating amelanotic and poorly differentiated melanomas in animals including humans which often elude definitive diagnosis and neoplasms that mimic melanoma microscopically. Smith discusses the use of different biomarkers, for example, vimentin, S100, NSE but cautions that these markers can be "found in a variety of tissues" non-specific for melanoma (p. 669, Col. 1, ¶12). Melan-A shows a narrow tissue distribution and has been studied in canine melanomas along with vimentin, S100, NSE expression. Smith states:

"It remains unproven that Melan-A expression is a predictor of less aggressive behavior, but it may be a worthwhile marker for identification of tumors of uncertain lineage, especially when used in combination with S100" (p. 669, Col. 2, ¶12),

and

"The advent of murine antibodies specific for melanoma-associated antigens, particularly melanosomes, has helped improve the value of IHC in the diagnosis of melanoma in human medicine. Often a panel of appropriate antibodies is advocated, an approach also favored in veterinary literature" (p. 670, Col. 1, ¶12),

and

"IBF is the first murine monoclonal antibody specifically created to recognize canine melanoma antigen and is highly sensitive (greater than 80%). Although it does cross-react with other types of neoplasia, such as basal cell tumors and lymphosarcomas, these neoplasms can easily be ruled out using additional immunohistochemical testing

and, on the whole, are not likely to be confused morphologically in the first instance (p. 679, Col. 1, ¶3).

Rutler et al. (Sem. Oncol. 29(4):370-381 (2002)) focused melanoma diagnostics for human patients relying on histopathological findings which AJCC-approved criteria for TNM classification and staging system of melanomas. Rutler teaches:

"A large number of molecular-biologic and immunohistochemical studies have sought new prognostic markers that identify patients at risk for local recurrence or metastatic disease. However, most of these markers are merely a reflection of tumor progression and do not improve the classic prognostic model that is based on evaluation of thickness, level of invasion, mitotic rate, ulceration, regression, and vascular invasion on routinely stained tissue sections...[but] a few molecules identifiable with immunohistochemistry have been claimed to carry additional prognostic significance" (p. 374, Col. 2, ¶2),

and these markers include integrins, MMP-2, VEGF, Mitf, and CD40 (pp. 374-375).

The conclusion to be drawn from these reviews for diagnosing malignant melanoma is that careful, detailed controls including sample control tissues and other art-recognized biomarkers for melanoma having a clinical stage-correlation for melanoma are required to practice the method invention. The ordinary artisan could not have practiced the claimed invention in order to unequivocally diagnose malignant melanoma in any subject using only GPC3 expression as the sole biomarker indicia. The ordinary artisan would not have had a reasonable expectation of success based on the prior art references and where the only marker is GPC3 and the method is performed in the absence of relevant control samples. For the above reasons, it appears that undue experimentation would be required to practice the claimed

invention.

Enablement

11. Claims 3, 5, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting GPC3 mRNA and/or cDNA in a sample from a melanoma patient, does not reasonably provide enablement for a diagnosing risk for malignant melanoma based on quantitating the GPC3 mRNA or cDNA much less in the absence of quantitating another art-recognized melanoma marker and that would allow a risk assessment of the subject to melanoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to a method for diagnosing a malignant melanoma comprising detecting or measuring GPC3 in a sample from a

subject at risk of having the cancer (Claim 3), or where the method of Claim 3 comprises quantifying GPC3 in a sample (Claim 5). Claim 8 is interpreted as being drawn to a method for diagnosing a malignant melanoma comprising a kit comprising a probe or a primer capable of detecting GPC3 expression. Claims 3 and 8 are interpreted as comprising detecting mRNA or cDNA for the expressed GPC3 gene using, for example, RT-PCR or microarray analysis.

The relative skill required to practice the invention is a clinical diagnostician performing clinical molecular diagnostic assays.

Disclosure in the Specification

The specification teaches and demonstrates detecting and quantifying GPC3 expressed message in human melanoma cell lines (Example 2) and tissues from malignant melanoma subjects (Example 3) using RT-PCR reaction according to Nakatsura et al. (Biochem. Biophys. Res. Commun. 281, 936-944 (2001); cited in the IDS of 11/13/07).

For human melanoma cell lines in Example 2, the GPC3 mRNA was detected using GPC3 PCR primers of SEQ ID NO: 3 and 4 and beta-actin primers as control standard. For human melanoma tissues in Example 3, GPC3 mRNA was compared in normal skin, human melanoma and human pigmented nevus tissues using the same primers. The specification does not describe a positive/negative control marker that distinguishes for example, a melanoma from a pigmented nevus, and therefore, a tissue-specific control/standard biomarker would seemingly be required to practice the

method where measuring the control marker mRNA or cDNA is required for qualitative and quantitative comparison.

The ordinary artisan could not practice the method to reliably, reproducibly and predictably diagnose a subject suspected of being at risk for malignant melanoma absent the use of specific molecular biological control reagents and control samples. The ordinary artisan would not have been enabled to practice the instant method at the time of the invention because the scope of the claims excludes several steps and reagents required to make a clinical molecular diagnosis for melanoma. Claim 3 embraces measurement of GPC3 nucleic acid by any method and the means to measure GPC3 expression is not even defined. The specification teaches that the detection of GPC3 in tissue samples of patients pre-diagnosed with melanoma is important for the present diagnostic method, i.e. to diagnose malignant melanoma in an early state compared to prior art diagnostic methods. However, the only biomarker considered in the entire diagnostic method is GPC3 and the ordinary artisan cannot even practice the instant claimed method without discriminating a melanoma from a heavily pigmented nevus using only the GPC3 mRNA transcript. The claims embrace any undisclosed probe or primer capable of detecting GPC3 message or cDNA in any sample yet the only primers disclosed as capable of being used in the RT-PCR are those of SEQ ID NOS: 3 and 4. The specification asserts common knowledge that RT-PCR can be used to detect the presence of a specific GPC3 mRNA population in a complex mixture of thousands of other mRNA species using the primers in Example 2 under the conditions described in Nakatsura without disclosing the cell or sample type.

Thus the claims do not meet the how-to-practice requirement under the enablement analysis for the full scope of embodiments.

Prior Art Status: Quantitative Gene Amplification by RT-PCR is Unpredictable Without Normalization

The specification does not disclose or enable the reference genes used to practice the method in a manner that would allow the ordinary artisan to predict that the subject was at risk for having malignant melanoma. The specification does not disclose a control condition to specifically identify and quantitate an expression level for the GPC3 nucleotide sequence in any patient sample. The importance of RT-PCR standardization more especially in for clinical diagnostics where for routine optimization is required is highly unpredictable based on the prior art.

Bergkvist et al. (Genet. Engineer. News 28(13):26 and 28 (July 2008)) specifically teach mRNA must be extracted and converted to cDNA by reverse transcription process and can produce a highly variable yield depending on the protocol. RNA is further rapidly degraded, and generally when assaying biological subjects, there is a need to minimize confounding technical and biological variability while maximizing the studies effect. Another caveat is the assay design (targeted sequence, the primers and the probe) which can give rise to a variation in the PCR efficiency among the studied genes, while any interfering substances inhibit PCR in a sample-dependent manner. The inset on p. 28 of Bergkvist identifies 8 variables that alone and in combination would reduce quantitative and qualitative assay efficiency.

Bustin et al. (Gen. Eng. News 29(14): 40-42 (8/1/09)) discuss the importance and

challenges for systemitizing quantitative RT-PCR especially regarding consistency between laboratories, where as in the present case, the clinical diagnostician should be reasonably assured of being enabled to replicate the method from amongst different clinical laboratories. Bustin states that "the MIQE guidelines stipulate full disclosure of reagents, protocols and analysis methods thus establishing that qPCR data meets a minimal set of standards. This increases confidence in its validity by ensuring that data meets a uniform quality benchmark..."; and Bustin appreciates for RT-qPCR, RNA quality can vary and that normalizing RT-qPCR results to reference genes without knowledge of the degradation status of the RNA could lead to incorrect conclusions.

The specification provides incomplete working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed, in the absence of a controlled RT-PCR reaction condition, with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Prior Art Status: Quantitative Hybridization Using Array Technology is Unpredictable

Claims 3 and 8 encompass the method of detecting GPC3 by a probe or primer in a microassay format where hybridization of GPC3 mRNA or cDNA to probes or primers arrayed on a solid support (e.g., gridding) in order to detect the presence of and to quantitate the level of gene expression. The specification does not so much as disclose a hybridization condition or a working example demonstrating quantitative

hybridization in an array method. Liang et al. (Funct. Integr. Genomics 6:1-13 (2006)) specifically teach that microarray results differ substantially among replicates and requires replication to increase the validity (p. 3, Col. 1, ¶1) and that the expression of a large number of irrelevant and redundant genes, the high level of noise in measurements and uncertainties in the data severely degrade both classification and prediction accuracy which require gene filtering and differentiation approaches to highlight the most relevant genes (p. 3, Col. 2, ¶2). Preston (Environ. Molec. Mutagenesis 45:214-221 (2005)) teaches "it is currently quite difficult to use microarray techniques to obtain quantitative assessments of gene expression; this is the result of the relatively nonquantitative nature of a number of steps in the process from total sample mRNA isolation and cDNA production to hybridization and detection. In addition, the method only detects transcripts that are relatively abundant in the cell. Thus microarray analysis is a useful tool for an initial survey of possible genes whose expression is altered, for example, by a chemical carcinogen...Additional RNA-based methods, such as real-time PCR or differential display, can be used to establish quantitative comparisons of expression among treatments, tissues, or organs for those genes identified as being interesting based on microarray analysis" (p. 217, Col. 1, ¶2 to Col. 1, ¶1).

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed, in the absence of a working example using a microarray, with a reasonable expectation of

success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Conclusion

12. No claims are allowed.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/

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Examiner, Art Unit 1643

Temporary Full Signatory Authority